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Structure function analysis of the actin ADP-ribosylating Clostridium  
botulinum C2 toxin

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JOURNAL: Naunyn-Schmiedeberg's Archives of Pharmacology 357 (4 SUPPL): p

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Experimental and Clinical Pharmacology and Toxicology Mainz, Germany  
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LANGUAGE: English

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0010047850 BIOSIS NO.: 199598515683

Mutations in the elongation factor 2 gene which confer resistance to diphtheria toxin and Pseudomonas exotoxin A: Genetic and biochemical analyses

AUTHOR: Foley Brian T; Moehring Joan M; Moehring Thomas J (Reprint)

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JOURNAL: Journal of Biological Chemistry 270 (39): p23218-23225 1995 

1995

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Both diphtheria toxin and Pseudomonas exotoxin A inhibit eukaryotic protein synthesis by **ADP**-ribosylating diphthamide, a posttranslationally modified histidine residue present in the elongation factor 2 (EF-2) protein. Elongation factor 2 cannot be **ADP**-ribosylated by the toxins unless this histidine is modified. In this report we identify three new point mutations in toxin-resistant alleles of the Chinese hamster ovary cell elongation factor 2 gene. The mutations resulted in amino acid substitutions at positions 584 (serine to glycine), 714 (isoleucine to asparagine), and 719 (glycine to aspartic acid). All three amino acid substitutions prevented the biosynthesis of diphthamide. The amount by which the toxins reduced protein synthesis in each of these mutant cell strains suggested that all three mutations also either impaired the function of EF-2 or reduced its steady state level in the cytoplasm. Western blot analysis showed that equal amounts of EF-2 were present in each of the cell strains, indicating that the mutations impaired the catalytic function of EF-2.

3855885 Genuine Article#: QL639 Number of References: 67  
Title: STRUCTURE AND FUNCTION OF **CLOSTRIDIUM**-BOTULINUM TOXINS  
Author(s): OGUMA K; FUJINAGA Y; INOUE K  
Corporate Source: OKAYAMA UNIV, SCH MED, DEPT BACTERIOL, 2-5-1 SHIKATA  
CHO/OKAYAMA 700//JAPAN/  
Journal: MICROBIOLOGY AND IMMUNOLOGY, 1995, V39, N3, P161-168  
ISSN: 0385-5600  
Language: ENGLISH Document Type: **REVIEW**

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04022001 Genuine Article#: QZ347 Number of References: 140

Title: MOLECULAR ASPECTS OF TETANUS AND BOTULINUM **NEUROTOXIN**  
POISONING

Author(s): AHNERTHILGER G; BIGALKE H

Corporate Source: FREE UNIV BERLIN, KLINIKUM BENJAMIN FRANKLIN, MEDKLIN &  
POLIKLIN, GASTROENTEROL ABT/W-1000 BERLIN//GERMANY//; HANNOVER MED  
SCH, INST TOXIKOL/HANNOVER//GERMANY/

Journal: PROGRESS IN NEUROBIOLOGY, 1995, V46, N1 (MAY), P83-96

ISSN: 0301-0082

Language: ENGLISH Document Type: **REVIEW**

Abstract: **Clostridial** neurotoxins, tetanus and the botulinum toxins

A-G, are high molecular weight proteins consisting of a heavy chain which is responsible for the internalisation and a light chain possessing a zinc-dependent proteolytic activity. They exclusively proteolyse either the vesicle membrane protein, synaptobrevin or two integral plasma membrane proteins, SNAP 25 and syntaxin. Together with cytosolic proteins these proteins form the SNARE complex involved in vesicle exocytosis, and their cleavage blocks the latter process.

**Clostridial** neurotoxins have now become powerful tools to investigate the final events occurring during secretion in neuronal, endocrine, and non-neuronal cells. They are applied to dissect the specific interactions of the SNARE protein complex with cytosolic fusogens and other modulators of exocytosis. Whereas exocytosis is not essential for the survival of cells, the organism as a whole will fall victim to a few nanograms since interneuronal and neuromuscular transmission is vital to muscular control, especially in respiration. Although all **clostridial** neurotoxins by their light chains attack proteins of the SNARE complex, tetanus **toxin** and the various botulinum toxins differ dramatically in their clinical symptoms. The biological information for this difference resides on the respective heavy chains which select different transport routes carrying the light chain from the place of entrance to the final compartment of action. So far the different transport vesicles used either by the various botulinum neurotoxins or by tetanus **toxin** are not yet defined. Nevertheless at least one of the botulinum toxins serves as a beneficial drug in the treatment of severe neuromuscular spasms.

Snake protein  
complex

03320862    Genuine Article#: NV897    Number of References: 105

Title: MECHANISM OF ACTION OF TETANUS AND BOTULINUM NEUROTOXINS

Author(s): MONTECUCCO C; SCHIAVO G

Corporate Source: UNIV PADUA,CNR,CTR BIOMEMBRANE,VIA TRIESTE 75/I-35121

PADUA//ITALY//; UNIV PADUA,DIPARTIMENTO SCI BIOMED/I-35121 PADUA//ITALY/

Journal: MOLECULAR MICROBIOLOGY, 1994, V13, N1 (JUL), P1-8

ISSN: 0950-382X

Language: ENGLISH    Document Type: **REVIEW**

**Abstract:** The **clostridial** neurotoxins responsible for tetanus and botulism are metallo-proteases that enter nerve cells and block neurotransmitter release via zinc-dependent cleavage of protein components of the neuroexocytosis apparatus. Tetanus **neurotoxin** (TeNT) binds to the presynaptic membrane of the neuromuscular junction and is internalized and transported retroaxonally to the spinal cord. Whilst TeNT causes spastic paralysis by acting on the spinal inhibitory interneurons, the seven serotypes of botulinum neurotoxins (BoNT) induce a flaccid paralysis because they intoxicate the neuromuscular junction. TeNT and BoNT serotypes B, D, F and G specifically cleave VAMP/synaptobrevin, a membrane protein of small synaptic vesicles, at different single peptide bonds. Proteins of the presynaptic membrane are specifically attacked by the other BoNTs: serotypes A and E cleave SNAP-25 at two different sites located within the carboxyl terminus, whereas the specific target of serotype C is syntaxin.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
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00435178 Genuine Article#: DR725 Number of References: 100

Title: **CLOSTRIDIAL** ADP-RIBOSYLTRANSFERASES - MODIFICATION OF  
LOW-MOLECULAR-WEIGHT GTP-BINDING PROTEINS AND OF ACTIN BY  
**CLOSTRIDIAL** TOXINS

Author(s): AKTORIES K

Corporate Source: UNIV ESSEN KLINIKUM, INST PHARMAKOL, HUFELANDSTR 55/D-4300  
ESSEN//FED REP GER/

Journal: MEDICAL MICROBIOLOGY AND IMMUNOLOGY, 1990, V179, N3, P  
123-136

Language: ENGLISH Document Type: **REVIEW**

6281301 Genuine Article#: YG152 Number of References: 225

Title: Pharmacologic characterization of botulinum **toxin** for basic science and medicine

Author(s): Pearce LB (REPRINT) ; First ER; MacCallum RD; Gupta A

Corporate Source: ASSOCIATED SYNAPSE BIOL, 11 HURLEY ST/CAMBRIDGE//MA/02141 (REPRINT); BOSTON UNIV, SCH MED, DEPT PHARMACOL & EXPT THERAPEUT/BOSTON//MA/02118

Journal: TOXICON, 1997, V35, N9 (SEP), P1373-1412

ISSN: 0041-0101 Publication date: 19970900

Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB

Language: English Document Type: **REVIEW**

**Abstract:** The use of Botulinum **neurotoxin** (BoNT) is increasing in both clinical and basic science. Clinically, intramuscular injection of nanogram quantities of BoNT is fast becoming the treatment of choice for a spectrum of disorders including movement disorders such as torticollis, blepharospasm, Meige Disease, and hemifacial spasm (Borodic et al., 1991, 1994a; Jankovic and Brin, 1991; Clarke, 1992). Neuroscientists are using BoNTs as tools to develop a better understanding of the mechanisms underlying the neurotransmitter release process. Consequently, our ability to accurately and reliably quantify the biologic activity of botulinum **toxin** has become more important than ever. The accurate measurement of the pharmacologic activity of BoNTs has become somewhat problematic with the most significant problems occurring with the clinical use of the toxins. The biologic activity of BoNTs has been measured using a variety of techniques including assessment of whole animal responses to in vitro effects on neurotransmitter release. The purpose of this review is to examine the approaches employed to characterize, quantify and investigate the actions of the BoNTs and to provide a guide to aid investigators in determining which of these methods is most appropriate for their particular application or use. (C) 1997 Elsevier Science Ltd.

06507052    Genuine Article#: YX893    Number of References: 64  
Title: Phylogeny and taxonomy of the food-borne pathogen **Clostridium**  
      botulinum and its neurotoxins  
Author(s): Collins MD (REPRINT) ; East AK  
Corporate Source: BBSRC, INST FOOD RES, DEPT MICROBIOL, EARLEY GATE,  
      WHITEKNIGHTS RD/READING RG6 6BZ/BERKS/ENGLAND/ (REPRINT)  
Journal: JOURNAL OF APPLIED MICROBIOLOGY, **1998**, V84, N1 (JAN), P5-17  
ISSN: 1364-5072    Publication date: 19980100  
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD, OXON,  
      ENGLAND OX2 ONE  
Language: English    Document Type: **REVIEW**



Review article

00781815 1998015655

Bacterial metalloprotease as the toxic factor in infection

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Journal: Journal of Toxicology - Toxin Reviews, 16/4 (177-194), 1997

, United States

PUBLICATION DATE: 19970000

CODEN: JTTRD

ISSN: 0731-3837

DOCUMENT TYPE: Review

LANGUAGES: English

SUMMARY LANGUAGES: English

NO. OF REFERENCES: 70

Metalloproteases, in which zinc metal ion is essential for catalytic activity, are produced by various human pathogenic bacteria. These metalloproteases have the consensus sequence HEXXH, in which two histidine residues function as the first and second zinc ligands. However, on the basis of the location of the third zinc ligand, they are classified into three families: the thermolysin, serralyisin and **neurotoxin** families. Members of the thermolysin family are synthesized as an inactive precursor with a N-terminal propeptide, and maturation of the precursor is achieved by several processing stages. The metalloprotease in the serralyisin family is generated without a conventional propeptide, and its transport is supported by additional secreted proteins. A wide variety of pathological actions of bacterial metalloproteases have been documented. In local bacterial infections, such as keratitis, dermatitis and pneumonia, the metalloprotease functions as a decisive virulence determinant. The protease generated at the site of the infection causes necrotic or hemorrhagic tissue damage through digestion of structural components of the ground substance. The protease also enhances vascular permeability and forms edematous lesions through generation of the inflammatory mediators, histamine and bradykinin. Additionally, permeability enhancement and/or tissue damage allows bacterial dissemination into the systemic circulation. In systemic infections such as septicemia, the metalloprotease acts as a synergistic virulence factor. The disordered proteolysis of many plasma

# Review article

01196387 Genuine Article#: GD367 Number of References: 90

Title: CELLULAR AND MOLECULAR ACTIONS OF BINARY TOXINS POSSESSING  
ADP-RIBOSYLTRANSFERASE ACTIVITY

Author(s): CONSIDINE RV; SIMPSON LL

Corporate Source: THOMAS JEFFERSON UNIV, JEFFERSON MED COLL, DEPT  
PHYSIOL/PHILADELPHIA//PA/19107; THOMAS JEFFERSON UNIV, JEFFERSON MED  
COLL, DEPT MED & PHARMACOL/PHILADELPHIA//PA/19107

Journal: TOXICON, 1991, V29, N8, P913-936

Language: ENGLISH Document Type: **REVIEW**

Abstract: **Clostridial** organisms produce a number of binary toxins.

Thus far, three complete toxins (botulinum, perfringens and spiroforme) and one incomplete **toxin** (difficile) have been identified. In the case of complete toxins, there is a heavy chain component (M(r) approximately 100,000) that binds to target cells and helps create a docking site for the light chain component (M(r) approximately 50,000). The latter is an enzyme that possesses mono(ADP-ribosyl)transferase activity. The toxins appear to proceed through a three step sequence to exert their effects, including a binding step, an internalization step and an intracellular poisoning step. The substrate for the toxins is G-actin. By virtue of ADP-ribosylating monomeric actin, the toxins prevent polymerization as well as promoting depolymerization. The most characteristic cellular effect of the toxins is alteration of the cytoskeleton, which leads directly to changes in cellular morphology and indirectly to changes in cell function (e.g. release of chemical mediators). Binary toxins capable of modifying actin are likely to be useful tools in the study of cell biology.

0014981851 BIOSIS NO.: 200400352640

Synaptotagmins I and II act as nerve cell receptors for botulinum

**neurotoxin G**

AUTHOR: Rummel Andreas; Karnath Tino; Henke Tina; Bigalke Hans; Binz Thomas  
(Reprint)

AUTHOR ADDRESS: Inst Biochem, Med Hsch Hannover, D-30625, Hannover, Germany  
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JOURNAL: Journal of Biological Chemistry 279 (29): p30865-30870, 30856

July 16, 2004 2004

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Botulinum neurotoxins (BoNTs) induce muscle paralysis by selectively entering cholinergic motoneurons and subsequent specific cleavage of core components of the vesicular fusion machinery. Complex gangliosides are requisite for efficient binding to neuronal cells, but protein receptors are critical for internalization. Recent work evidenced that synaptotagmins I and II can **function** as protein receptors for BoNT/B (Dong, M., Richards, D. A., Goodnough, M. C., Tepp, W. H., Johnson, E. A., and Chapman, E. R. ( 003) J. Cell Biol. 162, 1293-1303). Here, we report the protein receptor for a second BoNT serotype. Like BoNT/B, BoNT/G employs synaptotagmins I and II to enter phrenic nerve cells. Using pull-down assays we show that only BoNT/G, but neither the five remaining BoNTs nor tetanus **neurotoxin**, interacts with synaptotagmins I and II. In contrast to BoNT/B, interactions with both isoforms are independent of the presence of gangliosides. Peptides derived from the luminal domain of synaptotagmin I and II are capable of blocking the neurotoxicity of BoNT/G in phrenic nerve preparations. Pull-down and neutralization assays further established the membrane-juxtaposed 10 luminal amino acids of synaptotagmins I and II as the critical segment for **neurotoxin** binding. In addition, we show

12967957 Genuine Article#: 838SI Number of References: 72

Title: Large **clostridial** cytotoxins: cellular biology of  
Rho/Ras-glucosylating toxins

Author(s): Schirmer J; Aktories K (REPRINT)

Corporate Source: Univ Freiburg, Inst Expt Klin Pharmakol & Toxicol, Otto  
Kramer Haus, Albertstr 25/D-79104 Freiburg//Germany/ (REPRINT); Univ  
Freiburg, Inst Expt Klin Pharmakol & Toxicol, D-79104 Freiburg//Germany/(  
Klaus.Aktories@pharmakol.uni-freiburg.de)

Journal: BIOCHIMICA ET BIOPHYSICA ACTA-GENERAL SUBJECTS, 2004, V1673, N1-2  
(JUL 6), P66-74

ISSN: 0304-4165 Publication date: 20040706

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS

Language: English Document Type: **REVIEW**

Abstract: Mono-O-glycosylation of eukaryotic target proteins is the  
molecular mechanism of bacterial protein toxins of the family of large  
**clostridial** cytotoxins. This **toxin** family encompasses  
several high molecular mass proteins (>250 kDa) of various  
**Clostridia** species that are implicated in severe human diseases.  
**Toxin A** and **toxin B** from **Clostridium difficile** are  
the causative agents of pseudomembranous colitis and  
antibiotic-associated diarrhea. Lethal **toxin** and hemorrhagic  
**toxin** from **Clostridium sordellii** as well as alpha-  
**toxin** from **Clostridium novyi** are involved in the gas  
gangrene syndrome. The common mode of action of large **clostridial**  
cytotoxins is elicited by specific glycosylation of small GTP-binding  
proteins in the cytosol of target cells using activated nucleotide  
sugars as cosubstrates. Specific modification at a single threonine  
residue in the small GTPases renders these important key players of  
various signaling pathways inactive. This minireview intends to give an  
overview on structure-function analysis and mode of action of the large  
**clostridial** cytotoxins, as well as on the resulting functional  
consequences of glycosylation of target proteins. (C) 2004 Elsevier  
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Neurotoxins are subtoxins of the toxins that are claimed.